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Facilitation, Biophysical Models

Encyclopedia of Computational Neuroscience · Article ID: 348412 · Chapter ID: 347

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Synonyms

Short-term synaptic facilitation, frequency facilitation, paired-pulse facilitation, F1/F2 components of short-term synaptic enhancement

Definition

Facilitation is a temporary increase in postsynaptic response to a presynaptic action potential or depolarization induced by a preceding presynaptic depolarization. It is distinguished from longer-term components of activity-dependent synaptic enhancement by its low activation threshold (a pair of action potentials is often sufficient, hence the term paired-pulse facilitation) and short persistence time: facilitated response decays back to initial amplitude within less than a second after the stimulus train. Facilitation is very common in central and peripheral synapses of both vertebrate and invertebrate nervous systems; it is readily observed under conditions of low initial vesicle release probability, but is often occluded by synaptic depression when the initial vesicle release probability is sufficiently high. Biophysical models of facilitation go beyond a simple phenomenological description and often combine a model for presynaptic Ca^{2+} dynamics with a model of Ca^{2+} binding to exocytosis sites that trigger vesicle fusion.

Detailed Description

While postsynaptic effects can contribute to short-term enhancement of synaptic response, in most synapses facilitation is caused by some action of presynaptic Ca^{2+} ions entering during stimulation, which is intuitive in view of the steep non-linear dependence of baseline exocytosis rate on Ca^{2+} concentration ($[Ca^{2+}]$). However, simple whole-terminal elevation of Ca^{2+} is unlikely to fully explain this phenomenon because such accumulation is small compared to the high concentration of Ca^{2+} attained around an open Ca^{2+} channel and believed to be essential for triggering exocytosis (so-called Ca^{2+} nano- or micro-domains); considerable global Ca^{2+} accumulation is also inconsistent with the brief ("phasic") nature of synaptic response. Several alternative models for facilitation have been proposed, and are categorized below in terms of the respective physiological mechanism (see also reviews by Fioravante & Regehr, 2011; Zucker & Regehr, 2002). While mechanisms 1 and 2 listed below do not require a specialized facilitation site or process, mechanisms 3-5 rely on an extra Ca^{2+}-sensitive site which is either more remote from the Ca^{2+} channel, has a higher affinity for Ca^{2+}, or is slower than the fast low-affinity process responsible for baseline exocytosis and situated in close proximity to a Ca^{2+} channel. Detailed implementations biophysical models 2-5 include two ingredients: (1) model of Ca^{2+} dynamics (either a Partial Differential Equation for Ca^{2+} concentration, a stochastic Monte-Carlo simulation of Ca^{2+} ion movement, or a simplified Ordinary Differential Equation description), and (2) a model of Ca^{2+} binding to Ca^{2+} sensors controlling exocytosis and its facilitation (usually described by mass-action Ca^{2+}-binding reactions).

1. Activity-dependent increase in presynaptic Ca^{2+} influx

The most direct facilitation mechanism is provided by the activity-dependent increase in the Ca^{2+} current through presynaptic voltage-dependent Ca^{2+} channels during the stimulus train, observed in some synapses. Such increase can be either caused by depolarization directly (Bertram et al, 2003; Brody & Yue, 2000), or by Ca^{2+} entering as a result of such depolarization and activating second messengers such as calmodulin or neuronal calcium sensor proteins, which interact with the channels and increasing their conductance (Mochida, 2011). It is believed that this mechanism contributes to facilitation observed in certain conditions at the calyx of Held synaptic terminals (Catterall et al, 2013; Xu et al, 2007). However, in many synapses facilitation can be elicited without an increase in presynaptic Ca^{2+} current (Neher & Sakaba, 2008).

2. Facilitation of Ca^{2+} transients through buffer saturation.

The appealing property of the so-called buffer saturation mechanism is that it does not require any specialized facilitatory Ca^{2+}-binding site or process. Instead, facilitation in

this case is explained by direct increase in local microdomain free Ca^{2+} achieved in the vicinity of a Ca^{2+} channel during each successive action potential, caused by the progressive reduction of free buffer capacity as it is gradually depleted by Ca^{2+} entering during the conditioning pulses. First proposed on the basis of computational modeling (Klingauf & Neher, 1997; Neher, 1998a)this buffer saturation mechanism was recently shown to underlie facilitation at calbindin-positive neocortical and hippocampal synapses (Blatow et al, 2003; Burnashev & Rozov, 2005). Although the simplicity of this model is very appealing, it imposes strict requirements on the properties of the Ca^{2+} buffer; in particular, simulations show that buffer saturation should be achieved in a large portion of presynaptic terminal, which requires optimal concentrations of very fast and diffusible buffers (Matveev et al, 2004; Muller et al, 2005). Saturation of large concentration of immobile buffers would also lead to increase in Ca^{2+} transients, but would produce much more pronounced elevation of free residual Ca^{2+}, therefore immobile buffers arise more naturally when considering mechanism 4 below.

3. Bound residual Ca^{2+} accumulation

According to the bound residual Ca^{2+} model, facilitation results from the gradual increase in the Ca^{2+}-bound state of one or more Ca^{2+} sensors regulating exocytosis, rather than from an increase in free Ca^{2+} concentration, and therefore facilitation time course is entirely explained by the slow time scale of Ca^{2+} unbinding from these slow Ca^{2+} sensors that modulate exocytosis together with the fast Ca^{2+}-sensitive exocytosis trigger. This was historically the first conceptual model of facilitation first formulated by Katz and Miledi (1965) and Rahamimoff (1968), and realizations of this mechanism provided some of the first detailed models of facilitation (Yamada & Zucker, 1992; Bertram et al, 1996; Delaney & Tank, 1994; Dittman et al, 2000). To reconcile this mechanism with the observed sensitivity of facilitation to manipulations reducing free Ca^{2+} such as application of exogenous buffers, more up-to-date realistic implementation of this model involve simulations of free Ca^{2+} diffusion from the channel to the binding site, which confers to this model the required partial sensitivity to free Ca^{2+} (Yamada & Zucker, 1992; Bennett et al, 2004; Matveev et al, 2006; Nadkarni et al, 2010)

4. Free residual Ca^{2+} accumulation at a remote site (two-site model)

Although the growth of residual Ca^{2+} is small compared to the high Ca^{2+} concentration achieved in the vicinity of a Ca^{2+} channel-vesicle complex, it can still account for facilitation if exocytosis is assumed to be controlled by two independent Ca^{2+}-sensitive processes, one of which is located close to the vesicle location and controlled by fast microdomain Ca^{2+} transients coinciding with each action potential, and another lower-affinity Ca^{2+} sensitive process located further away from the channel (perhaps shielded by the vesicle itself or other diffusion barrier), where the small accumulation of residual Ca^{2+} is comparable to the smaller peak Ca^{2+} reaching this more remote location. Thus, this model can be referred to as a *two-site model*. It should be noted that the presence of fixed buffers can aid in residual Ca^{2+}accumulation, since immobile Ca^{2+} buffers act as a Ca^{2+} trap, binding Ca^{2+} close to the vesicle-channel complex and slowly releasing it between action potentials (Neher, 1998b). Biophysical implementations of the two-site model require simulations of Ca^{2+} diffusion and buffering (Matveev et al, 2002; Tang et al, 2000).

5. Ca-dependent acceleration of vesicle mobilization

Vesicles undergo several biochemical steps such as docking and priming before becoming competent for exocytosis, and like exocytosis itself, these steps are Ca^{2+}-dependent. Therefore, facilitation may arise from acceleration of such “vesicle pool mobilization” in response to Ca^{2+} elevation, increasing the number of vesicles available for release, rather than increasing the probability of release of any individual vesicle (Sorensen, 2004; Neher & Sakaba, 2008). This mechanism would also explain acceleration of recovery from short-term synaptic depression observed in several synapses (Dittman & Regehr, 1998; Stevens & Wesseling, 1998; Wang & Kaczmarek, 1998; Hosoi et al., 2007). It is possible that the last priming steps involves a geometric change in the active zone morphology, reducing the channel-vesicle distance (Gentile & Stanley, 2005; Wadel et al, 2007), an effect termed “positional priming” (Neher & Sakaba, 2008).

Although these effects are biologically very different from mechanisms discussed earlier, corresponding facilitation models share formal similarities with both the two-site model and the bound Ca^{2+} model discussed above. Namely, like in the two-site model, exocytosis is dependent on the combined action of two separate Ca^{2+}-sensitive processes, with the fast low-affinity exocytosis process sensing microdomain Ca^{2+} and ensuring phasic synaptic response, and the second high-affinity “priming” process responsible for facilitation controlled by smaller elevations of global Ca^{2+} outside of the microdomain. This mechanism also shares the characteristic property of the bound-Ca^{2+} model in that exocytosis is not in instantaneous equilibrium with local Ca^{2+} concentration, since the priming reactions are at best only slowly reversible. Earlier

models of Ca^{2+}-dependent mobilization are based on ordinary differential equations (Dittman et al, 2000; Worden et al, 1997), with more recent models incorporate Ca^{2+} diffusion and buffering to account for the pronounced effects of Ca^{2+} buffering on synaptic facilitaiton (Millar et al, 2005; Pan & Zucker, 2009).

We note that the above mechanisms are not mutually exclusive, and several of them may contribute to facilitation at a particular synaptic terminal. For example, in one of the most detailed recent studies of exocytosis and its short-term plasticity involving stochastic Monte-Carlo simulations of Ca^{2+} ion dynamics (Nadkarni et al, 2010; Nadkarni et al, 2012), both free and bound residual Ca^{2+} accumulation contributes to facilitation.

Other Models

A more controversial possibility is that exocytosis depends on voltage explicitly apart from its Ca^{2+} dependence (the so-called “calcium-voltage hypothesis”). Assuming that the exocytosis sensor is shielded from the high Ca^{2+} microdomain, small residual Ca^{2+} accumulation is comparable to peak^{2+} Ca achieved during the action potential and therefore would be sufficient for facilitation (Parnas et al, 1986). Therefore, this mechanism can be viewed as a modification of the free residual Ca^{2+} accumulation model (mechanism 4).

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